

REMARKS

Claims 1 to 12, as amended, appear in this application for the Examiner's review and consideration. The amendments are fully supported by the specification and claims as originally filed. Therefore, there is no issue of new matter. In addition, the amendments to the independent claims add recitations that elaborate on the structure of the presently claimed invention, and, thus, do not affect the scope of the claims. The amendments only further clarify the claimed invention.

Claims 1 to 12 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hayes, 6.2.2.1, Selective Precipitation, IUPAC Compendium of Chemical Terminology, (IUPAC), chm.vt.edu (VT), Angel C. de Dios, Le Chateli  s Principle, Lecture VIII, Chem 056 (de Dios), Complexation and Precipitation Titrations (Complexation), Volumetric (Titrametric) Analysis (Volumetric Analysis), Protein Purification Handbook (the Handbook), and Solubility of Ionic Salts in Water: Precipitation Titrations (Ionic Salts) for the reasons set forth on pages 2 and 3 of the Office Action.

In response, Applicants again submit that neither the present Office Action nor any of the previous Office Actions for this application have cited any reference regarding zoledronic acid, and, in particular, the Office Actions fail to cite any reference directed to the purification of zoledronic acid.

The presently claimed invention is directed to a process for purifying zoledronic acid comprising (a) raising the pH of an aqueous suspension of crude zoledronic acid until a clear solution is obtained; (b) lowering the pH of the solution obtained in (a) until purified zoledronic acid precipitates out of solution; and (c) isolating the purified zoledronic acid that has precipitated from the solution in (b). As will be recognized by one of ordinary skill in the art, the presently claimed invention will only work if the impurities contained in crude zoledronic acid are more soluble in an acidic solution than is zoledronic acid.

Therefore, to be within the scope of the present claims, a prior art reference must disclose or suggest that crude zoledronic acid can be purified with the process of the presently claimed invention. For the zoledronic acid to be purified in the process of the present invention, impurities found in zoledronic acid must not precipitate with the zoledronic acid when the zoledronic acid solution is acidified. That is, the impurities found in crude zoledronic acid must be more soluble than zoledronic acid in an acidic solution. Thus, to render the present claims obvious, one or more prior art references must disclose or suggest that impurities found in crude zoledronic acid are more soluble than zoledronic acid

in acidic solution, and do not precipitate with the zoledronic acid when the pH of a clear solution of zoledronic acid is lowered until purified zoledronic acid precipitates, where the clear solution is formed by raising the pH of an aqueous suspension of crude zoledronic acid, as presently claimed. As none of the cited references disclose or suggest anything regarding zoledronic acid or the impurities found in the acid, the cited references do not disclose or suggest anything regarding the relative solubilities of zoledronic acid and the impurities contained in crude zoledronic acid, and the present claims are not obvious over the cited references.

In particular, the cited references disclose general principles regarding acid-base chemistry, Le Chateli  rs Principle, titrations, etc. Therefore, the cited references disclose that the pH of a solution changes when an acid or base is added, that the mass balance in an equilibrium can be changed by adding a reactant or a product, and that, during a titration, a product may, but does not necessarily, precipitate. However, none of the cited references disclose or suggest that the disclosed principles can be used to purify any specific acid, and, in particular, do not disclose or suggest that the disclosed principles can necessarily be used to purify zoledronic acid.

Although one of ordinary skill in the art will understand that Le Chateli  rs Principle states that the mass balance of an equilibrium shifts in response to the addition or removal of a material from either side of the equilibrium, one of ordinary skill in the art will understand that the properties of the equilibrium depend on the materials in the equilibrium. In some cases, no precipitate is formed, and the equilibrium remains in balance. In other cases, a precipitate forms that makes the reverse reaction impossible. In other cases, the precipitate can be placed in solution again by varying the properties of the reaction mixture.

However, Le Chateli  rs Principle by itself, or even taken with other general principles, does not disclose specific properties of any specific system, such as a suspension of a particular crude insoluble acid, containing impurities, where at least the acid can be dissolved by raising the pH of the suspension. Applicants again submit that none of the general principles discussed in the cited references, including Le Chateli  rs Principle, disclose or suggest anything regarding any specific acid, and, in particular, do not disclose or suggest anything regarding the relative solubilities of zoledronic acid and the impurities found in crude zoledronic acid. As the cited references do not disclose or suggest that the impurities found in crude zoledronic acid are more soluble than zoledronic acid in an acidic solution, the cited references do not disclose or suggest that crude zoledronic acid can be purified with the presently claimed invention.

Thus, none of the cited references disclose or suggest that zoledronic acid can be purified by raising the pH of an aqueous suspension of crude zoledronic acid until a clear solution is obtained, lowering the pH of the solution until purified zoledronic acid precipitates out of solution, and isolating the precipitated purified zoledronic acid, as presently claimed.

Hayes discloses the selective precipitation of metal ions from leach solutions by changing the pH of the solution. Hayes at page 251. However, Hayes, whether taken alone or in combination with the other references, does not disclose or suggest anything regarding zoledronic acid or the relative solubilities of zoledronic acid and the impurities found in crude zoledronic acid, and, thus, does not disclose or suggest raising the pH of an aqueous suspension of crude zoledronic acid until a clear solution is obtained, lowering the pH of the solution until purified zoledronic acid precipitates out of solution, and isolating the precipitated purified zoledronic acid, as presently claimed. Therefore, the present claims are not obvious over Hayes, whether taken alone or in combination with the other references.

As stated in the Office Action IUPAC and VT define precipitation titrations. However, IUPAC and VT, whether taken alone or in combination with the other references, do not disclose or suggest anything regarding zoledronic acid or the relative solubilities of zoledronic acid and the impurities found in crude zoledronic acid, and, thus, do not disclose or suggest raising the pH of an aqueous suspension of crude zoledronic acid until a clear solution is obtained, lowering the pH of the solution until purified zoledronic acid precipitates out of solution, and isolating the precipitated purified zoledronic acid, as presently claimed. Therefore, the present claims are not obvious over those references, whether taken alone or in combination with the other references.

De Dios discloses the principle of chemical equilibrium with regard to Le Chatelier's Principle. However, de Dios, whether taken alone or in combination with the other references, does not disclose or suggest anything regarding zoledronic acid or the relative solubilities of zoledronic acid and the impurities found in crude zoledronic acid, and, thus, does not disclose or suggest raising the pH of an aqueous suspension of crude zoledronic acid until a clear solution is obtained, lowering the pH of the solution until purified zoledronic acid precipitates out of solution, and isolating the precipitated purified zoledronic acid, as presently claimed. Therefore, the present claims are not obvious over de Dios, whether taken alone or in combination with the other references.

Complexation and Volumetric Analysis also disclose titrations for the determination of the concentration of a dissolved material. However, those references, whether taken alone or in combination with the other references, do not disclose or suggest anything regarding

zoledronic acid or the relative solubilities of zoledronic acid and the impurities found in crude zoledronic acid, and, thus, do not disclose or suggest raising the pH of an aqueous suspension of crude zoledronic acid until a clear solution is obtained, lowering the pH of the solution until purified zoledronic acid precipitates out of solution, and isolating the precipitated purified zoledronic acid, as presently claimed. Therefore, the present claims are not obvious over Complexation and Volumetric Analysis, whether taken alone or in combination with the other references.

The Handbook discloses various strategies for the purification of proteins. However, the Handbook, whether taken alone or in combination with the other references, does not disclose or suggest anything regarding zoledronic acid or the relative solubilities of zoledronic acid and the impurities found in crude zoledronic acid, and, thus, does not disclose or suggest raising the pH of an aqueous suspension of crude zoledronic acid until a clear solution is obtained, lowering the pH of the solution until purified zoledronic acid precipitates out of solution, and isolating the precipitated purified zoledronic acid, as presently claimed. Therefore, the present claims are not obvious over the Handbook, whether taken alone or in combination with the other references.

The reference Ionic Salts defines titrations, and discloses the determination of chloride ion concentration by titration with silver ion. However, Ionic Salts, whether taken alone or in combination with the other references, does not disclose or suggest anything regarding zoledronic acid or the relative solubilities of zoledronic acid and the impurities found in crude zoledronic acid, and, thus, does not disclose or suggest raising the pH of an aqueous suspension of crude zoledronic acid until a clear solution is obtained, lowering the pH of the solution until purified zoledronic acid precipitates out of solution, and isolating the precipitated purified zoledronic acid, as presently claimed. Therefore, the present claims are not obvious over Ionic Salts, whether taken alone or in combination with the other references.

Moreover, Applicants submit that one of ordinary skill in the art would not be motivated to obtain and/or practice the presently claimed invention based on what is generally known and available in the pertinent art. In this regard, as discussed in the present specification at page 2, lines 9 to 15, and page 4, lines 28 to 32, the prior art teaches that zoledronic acid can be purified by recrystallization from water, requiring reflux temperatures and large quantities of water. No other process is practiced in the prior art. The prior art does not disclose any other means of purifying zoledronic acid. As a result, the purification of zoledronic acid, as practiced prior to the present invention, requires a significantly higher temperature and a significantly greater amount of water than is required with the presently

claimed process. As the prior art teaches that zoledronic acid must be crystallized from water at high temperature for purification, and does not disclose or suggest the presently claimed process, the prior art provides no motivation for one of ordinary skill in the art to obtain and/or practice the presently claimed invention.

As set forth in M.P.E.P § 2141 I,

Patent examiners carry the responsibility of making sure that the standard of patentability enunciated by the Supreme Court and by the Congress is applied in each and every case. The Supreme Court in *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966), stated:

Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or non-obviousness, these inquires may have relevancy...

This is not to say, however, that there will not be difficulties in applying the nonobviousness test. What is obvious is not a question upon which there is likely to be uniformity of thought in every given factual context. The difficulties, however, are comparable to those encountered daily by the courts in such frames of reference as negligence and scienter, and should be amenable to a case-by-case development. We believe that strict observance of the requirements laid down here will result in that uniformity and definiteness which Congress called for in the 1952 Act.

Office policy is to follow *Graham v. John Deere Co.* in the consideration and determination of obviousness under 35 U.S.C. 103. As quoted above, the four factual inquires enunciated therein as a background for determining obviousness are as follows:

- (A) Determining the scope and contents of the prior art;
- (B) Ascertaining the differences between the prior art and the claims in issue;
- (C) Resolving the level of ordinary skill in the pertinent art; and
- (D) Evaluating evidence of secondary considerations.

Therefore, to establish a *prima facie* case of obviousness, the following are required:

- A) A determination of the scope and content of the prior art;
- B) An ascertainment of the prior art and the claims in issue;
- C) A resolution of the level of ordinary skill in the pertinent art; and
- D) An evaluation of the *Graham* secondary considerations.

In the present case, as discussed above, a determination of the scope and contents of the prior shows that the prior art does not disclose or suggest the purification of zoledronic

acid with the presently claimed process. Instead, the prior art teaches recrystallizing zoledronic acid in water at reflux temperatures. Applicants submit that there are no known prior art references that disclose or suggest the presently claimed process for purifying zoledronic acid.

An ascertainment of the differences between the prior art and the claims at issue shows the following:

The present claims are directed to a process for purifying zoledronic acid, comprising:

- (a) raising the pH of an aqueous suspension of crude zoledronic acid until a clear solution is obtained;
- (b) lowering the pH of the solution obtained in (a) until purified zoledronic acid precipitates out of solution; and
- (c) isolating the purified zoledronic acid that has precipitated from the solution in (b).

In contrast, the prior art teaches purifying zoledronic acid using recrystallization in water at reflux temperature. Therefore, the present claims are significantly and patentably different from the prior art.

With regard to the level of ordinary skill in the pertinent art, at the time of the present invention, one of ordinary skill in the art, based on the teachings of the prior art, would have understood that zoledronic acid was purified by recrystallizing the zoledronic acid from water at reflux temperatures. There was no other teaching in the art regarding the purification of zoledronic acid at that time.

Finally, an evaluation of the secondary considerations shows that, at the time of the present invention, zoledronic acid was purified by recrystallizing the zoledronic from water at reflux temperatures. As a result, the only process known and used in the prior art requires significantly higher temperatures and significantly greater amounts of water than are required with the presently claimed invention. Reductions in operating temperature and the amount of water required are clearly desirable, particularly in industrial production. However, there is no known prior art disclosure of the purification of zoledronic acid using the presently claimed process. That is, prior to the presently claimed invention, there was an unsolved need to reduce the temperature at which zoledronic acid is purified, and to reduce the amount of water required for the purification, particularly in industrial production. However, prior to the presently claimed invention, such a method was not known or used. This is a clear indication of non-obviousness, as set forth in *Graham*.

Therefore, as there is no evidence that the cited references are prior art to the present application, and the cited references do not disclose or suggest the presently claimed invention, the present claims are not obvious. Accordingly, it is respectfully requested that the Examiner withdraw the rejection of claims 1 to 12 over the cited references.

Applicants thus submit that the entire application is now in condition for allowance, an early notice of which would be appreciated. Should the Examiner not agree with Applicants' position, a personal or telephonic interview is respectfully requested to discuss any remaining issues prior to the issuance of a further Office Action, and to expedite the allowance of the application.

A separate Extension of Time Fee Sheet is submitted herewith. Should any other fees be required, however, please charge such fees to Deposit Account No. **11-0600**.

Respectfully submitted,

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